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Comparative Accuracy of Real-Time Myocardial Contrast Perfusion Imaging and Wall Motion Analysis During Dobutamine Stress Echocardiography for the Diagnosis of Coronary Artery Disease

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OBJECTIVE This study sought to compare the accuracy of myocardial contrast echocardiography (MCE) and wall motion analysis (WMA) during submaximal and peak dobutamine stress echocardiography (DSE) for the diagnosis of coronary artery disease (CAD).

BACKGROUND The relative merits of MCE and WMA for the detection of CAD during DSE have not been studied in a large number of patients.

METHODS We studied 170 patients who underwent dobutamine (up to 50 μg/kg/min)-atropine stress testing and coronary angiography. The WMA and MCE (using repeated boluses of Optison [Mallinckrodt, St. Louis, Missouri] or Definity [Bristol-Myers Squibb, New York, New York]) were performed at rest, at intermediate stress (65% to 75% of maximal heart rate), and at peak stress. The diagnosis of CAD (≥50% stenosis in ≥1 coronary artery) was based on reversible wall motion and perfusion abnormalities.

RESULTS Coronary artery disease was detected in 127 (75%) patients. Sensitivity of MCE was higher than that of WMA at maximal stress (91% vs. 70%; $p = 0.001$) and at intermediate stress (84% vs. 20%; $p = 0.0001$). Specificity was lower for MCE compared with WMA (51% vs. 74%; $p = 0.01$). Overall accuracy was higher for MCE than for WMA (81% vs. 71%; $p = 0.01$). Sensitivity for detection of CAD based on abnormalities in ≥2 vascular regions was higher for MCE than for WMA (67% vs. 28%; $p < 0.01$).

CONCLUSIONS The majority of inducible perfusion abnormalities occur at an intermediate phase of the stress test, without wall motion abnormalities. Myocardial contrast echocardiography provides better sensitivity than WMA, particularly in patients with submaximal stress and in identifying patients with multivessel CAD. (J Am Coll Cardiol 2004;44:2185–91) © 2004 by the American College of Cardiology Foundation

Dobutamine stress echocardiography (DSE) is a widely used technique for the diagnosis of coronary artery disease (CAD). However, pooled data have shown that the sensitivity of wall motion analysis (WMA) is modest, particularly in patients with single-vessel CAD (1–7). Although patients with multivessel CAD often demonstrate wall motion abnormalities during DSE, abnormalities are often detected in a single vascular region, with underestimation of the extent of CAD (1).

The induction of new wall motion abnormalities during DSE is largely dependent on achieving an adequate stress level. Failure to achieve the predicted heart rate has been associated with false negative tests (1,5,8). Experimental studies have shown that myocardial perfusion abnormalities precede wall motion abnormalities during dobutamine infusion and, therefore, assessment of myocardial perfusion may potentially improve the sensitivity of DSE in patients with submaximal stress (9). Despite evidence from animal studies, the temporal sequence of perfusion and functional abnormalities in the ischemic cascade has not been adequately studied in humans.

Myocardial contrast echocardiography (MCE) is a newly introduced technique for the evaluation of myocardial perfusion in patients with suspected CAD (10–21). Real-time imaging using low mechanical index pulse sequence schemes enhances the detection of microbubbles and reduces microbubbles' destruction. This permits the real-time identification of perfusion abnormalities during stress echocardiography (21). The aims of this prospective study were: 1) to compare the accuracies of MCE and WMA during DSE for the overall and regional diagnosis of CAD; 2) to study the impact of achieved stress level on the accuracy of both methods; and 3) to document the temporal sequence of perfusion and wall motion abnormalities during myocardial ischemia in a large number of patients with suspected CAD.

METHODS

We prospectively studied 1,318 patients with known or suspected CAD, referred for DSE, by real-time MCE in conjunction with WMA in our institution between January

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
DSE = dobutamine stress echocardiography
ECG = electrocardiogram
LAD = left anterior descending
LCx = left circumflex
MCE = myocardial contrast echocardiography
RCA = right coronary artery
WMA = wall motion analysis

2000 and July 2003. Among these patients, 179 underwent coronary angiography within one month of DSE. Nine (5%) patients were excluded because of contrast attenuation during DSE that precluded adequate analysis of wall motion and perfusion. The final population, therefore, consisted of 170 patients. Mean age was 60 ± 12 years. There were 71 (42%) women. All patients gave an informed consent to undergo the stress test. The protocol of this study was approved by the Institutional Review Board of the University of Nebraska Medical Center. Clinical data are presented in Table 1.

Dobutamine stress test. Patients were instructed to discontinue beta-blockers 24 h before the stress test. Dobutamine was infused at a starting dose of 5 μg/kg/min for 3 to 5 min, followed by 10 μg/kg/min for 3 to 5 min. The dobutamine dose was increased by 10 μg/kg/min every 3 min up to a maximum dose of 50 μg/kg/min. Atropine (up to 2 mg) was administered intravenously if 85% of maximal predicted heart rate (220 − age) was not achieved. End points were achievement of target heart rate, maximal dose of dobutamine and atropine, hypertension (blood pressure >240/120 mm Hg), symptomatic decrease in systolic blood pressure, symptomatic or sustained ventricular or supraventricular tachycardia, ST-segment depression >2 mm in electrocardiogram (ECG) leads without resting ST-segment depression, >2 mm ST-segment elevation in ECG leads without Q waves, severe angina, and any intolerable adverse effect considered to be the result of dobutamine or atropine. Metoprolol (1 to 5 mg) was used intravenously to reverse the side effects of dobutamine if these did not revert quickly after termination of the infusion.

Table 1. Clinical Data of the Study Patients

Clinical Parameters	Number (%)
Reasons for referral	
Evaluation of chest pain	108 (64%)
Multiple risk factors	14 (8%)
Peri-operative risk assessment	48 (28%)
Previous myocardial infarction	39 (23%)
Diabetes mellitus	23 (14%)
Hypertension	124 (73%)
Hypercholesterolemia	107 (63%)
Cigarette smoking	61 (36%)
Beta blockers	137 (81%)
Calcium channel blockers	57 (34%)
Ejection fraction	60 ± 14%

Echocardiographic imaging. The contrast agents used for the study were a perfluorocarbon-containing, albumin-coated microbubble (Optison, Mallinckrodt, St. Louis, Missouri) in 140 patients and a lipid-encapsulated, perfluoropropane-filled microbubble (Definity, Bristol-Myers Squibb, New York, New York) in 30 patients. Imaging was performed using commercially available ultrasound scanners (Philips Agilent 5500 B.2 and Philips ATL HDI 5000 10.3.5, Philips Medical Systems, Bothell, Washington; or Siemens Acuson Sequoia 6.0, Siemens Medical Solutions, Malvern, Pennsylvania), equipped with low mechanical index, real-time pulse sequence schemes. Imaging was performed by the use of pulse-inversion Doppler (Philips ATL) in 109 (64%) patients, contrast pulse sequencing (Siemens Acuson Sequoia) in 30 (18%) patients, and power modulation (Philips Agilent) in 31 (18%) patients. The equipment was adjusted to achieve maximal nonlinear signal from contrast. Mechanical indexes were set to ≤0.3 and frame rate to ≥25 Hz. Time-gain compensation and two-dimensional gain settings were adjusted to suppress signals from the myocardium before contrast injection. Images from apical views (four-, two-, and three-chamber) were obtained and digitized at rest; at an intermediate stage of stress, defined as achievement of 65% to 75% of maximal heart rate predicted for age and at maximal stress after the patients had achieved ≥85% predicted maximum heart rate or a test end point.

After optimization of the settings, a 0.2- to 0.3-ml calibration dose of Optison or a 0.1- to 0.15-ml dose of Definity followed by a saline flush was given. Setting corrections were made to optimize gain and minimize any tissue nonlinear signals. Imaging began with a similar contrast dose in the apical four-chamber view. A minimum of 15 s of image acquisition was performed after peak myocardial opacification until disappearance of contrast from the myocardium. Imaging was acquired from the apical two-chamber and apical long axis views using the same method.

An independent investigator who had no knowledge of the clinical and angiographic data interpreted wall motion and perfusion using the 16-segment model (1). Studies were interpreted as either normal or abnormal in each of the three coronary arterial territories. A stress-induced contrast defect was considered present when two contiguous segments failed to exhibit contrast enhancement during the washout of contrast after the bolus injection compared with other segments at the same depth in the same view, and compared with contrast enhancement in the same segment at rest using a side-by-side image analysis. Attenuation from contrast or lung interference was considered present if any segment could not be visualized and was not distinguishable from surrounding tissue.

Wall motion was scored in each of the 16 segments as normal, hypokinetic, akinetic, or dyskinetic. A positive test

for wall motion was defined as new or worsening wall motion abnormality in two or more contiguous segments during stress. The interobserver agreement in our laboratory is 84% for MCE and 91% for WMA (21). Intraobsever agreement was determined at intermediate and at peak stress for both WMA and MCE in 30 randomly selected patients. Results were presented as a percentage with a corresponding kappa value. To assess the accuracy of the independent reviewer for wall motion analysis of a standard DSE without contrast, 30 randomly selected patients who underwent standard DSE using the same infusion protocol and who had coronary angiography were evaluated.

The anterior septum, mid-posterior septum, anterior wall, and adjacent apical segments were assigned to the left anterior descending (LAD) coronary artery, lateral segments to the left circumflex (LCx) artery, and inferior and basal septal segments to the right coronary artery (RCA). The posterior wall was considered an overlap region and was assigned to either the LCx or RCA distribution. The apical inferior/posterior segments were also considered overlap regions and were assigned to the vascular territory with contiguous abnormalities.

Quantitative angiography. Coronary angiography was performed within one month of DSE using the Judkins technique. Left ventriculography was performed to calculate ejection fraction. Quantitative measurements of coronary artery stenosis were made by an experienced interventional cardiologist (who had no knowledge of DSE results) using a hand-held electronic caliper (Tesa SA, Renens, Switzerland) (22). Measurements were expressed as the percent diameter narrowing, using the diameter of the nearest normal-appearing region as a reference. Coronary artery narrowings of ≥50% and ≥70% diameter were both used as cutoff values.

Statistical analysis. Continuous variables were presented as mean and standard deviation and were compared using the Student *t* test. Sensitivity, specificity, and accuracy were calculated using standard definitions and were presented with 95% confidence intervals (CI). Comparison of proportions was made by the chi-square test. A p value <0.05 was considered significant.

RESULTS

Coronary angiography. Coronary artery disease (≥50% stenosis) was detected in 127 (75%) patients. Among these patients, 32 had single-vessel, 50 had two-vessel, and 45 had three-vessel CAD. The remaining 43 patients had no significant CAD. Coronary artery stenoses involved the LAD in 101 (59%), the RCA in 82 (48%), and the LCx in 84 (49%) patients.

Dobutamine stress test. Dobutamine-atropine induced significant changes in heart rate and rate pressure product (Table 2). Atropine was administered in 148 (87%) patients with a mean dose of 0.6 ± 0.5 mg. Chest pain occurred in 96 (56%) patients and ST-segment depression (>0.1 mV horizontal or downsloping) occurred in 32 (19%) patients.

Table 2. Hemodynamic Data at Different Stages of the Dobutamine Stress Test

Stage	Heart Rate (beats/min)	Rate-Pressure Product	Dobutamine Dose (μg/kg/min)
Rest	74 ± 13	11,473 ± 9,466	0
Intermediate	111 ± 11	16,975 ± 5,715	24 ± 10
Peak	144 ± 10	21,373 ± 5,487	32 ± 8

The target heart rate was achieved in 143 (84%) patients. Reasons for termination of the test in other patients were severe angina in eight patients, ST-segment changes in four patients, hypotension in one patient, and severe dyspnea in one patient. The test was not terminated because of wall motion or perfusion abnormalities in any patient.

New or worsening wall motion abnormalities occurred in 100 (59%) patients. Among these patients, 17 (17%) patients had resting abnormalities as well. New wall motion abnormalities were observed at intermediate stress in 27 patients. Inducible myocardial perfusion abnormalities occurred in 138 (81%) patients. These abnormalities were observed at intermediate stress in 119 (70%) patients. The intraobserver agreement on the presence or absence of reversible perfusion abnormality was 90% at intermediate stage (Kappa = 0.77) and 92% at peak stress (Kappa = 0.84). The intraobserver agreement on the presence or absence of inducible wall motion abnormality was 93% at intermediate stage (Kappa = 0.63) and 92% at peak stress (Kappa = 0.81).

Diagnostic accuracy of MCE and WMA. Inducible myocardial perfusion abnormalities were detected in 116 of 127 patients with a ≥50% stenosis of ≥1 coronary artery and in 21 of 43 patients without a significant stenosis. New or worsening wall motion abnormalities were detected in 89 of 127 patients with ≥50% stenosis of ≥1 coronary artery and in 11 of 43 patients without a significant stenosis. Sensitivity, negative predictive value, and accuracy of MCE were significantly higher than for WMA. The difference in sensitivity was more striking at the intermediate stage. Specificity was higher for WMA (Table 3). The positive predictive value tended to be higher for WMA, but this difference did not reach statistical significance. Coronary artery disease was detected in 21 patients who received Definity and in 106 patients who received Optison. There was no significant difference between Optison and Definity with regard to sensitivity (92%, 95% confidence interval [CI] 0.87 to 0.98 vs. 86%, 95% CI 0.71 to 1.0), specificity (50%, 95% CI 0.33 to 0.67 vs. 56%, 95% CI 0.23 to 0.88), or accuracy (82%, 95% CI 0.76 to 0.89 vs. 77%, 95% CI 0.62 to 0.92).

Diagnostic accuracy of MCE based on the echocardiographic system was 78% for Philips Agilent, 83% for Philips ATL, and 77% for Siemens Acuson Sequoia (p = NS).

Among the 30 randomly selected patients who underwent DSE without contrast, CAD was detected by angiography in 19. Sensitivity of WMA was 74% (95% CI 0.54 to

Table 3. Overall Accuracy of Myocardial Contrast Echocardiography and Wall Motion Analysis for the Diagnosis of Coronary Artery Disease (≥50% Stenosis)

Diagnostic Parameters	Myocardial Contrast	Wall Motion	p
Sensitivity at peak stage	91% (86–96)	70% (62–78)	0.001
Sensitivity at intermediate stage	84% (78–91)	20% (13–27)	0.0001
Sensitivity in single-vessel CAD	81% (68–95)	53% (63–70)	0.001
Sensitivity in multi-vessel CAD	95% (90–99)	76% (66–84)	0.001
Specificity	51% (36–66)	74% (61–88)	0.01
Positive predictive value	85% (79–91)	89% (83–95)	0.09
Negative predictive value	67% (59–75)	46% (36–56)	0.02
Accuracy	81% (75–87)	71% (64–78)	0.01

Diagnostic parameters are presented as % with corresponding 95% confidence intervals.

0.94), specificity was 82% (95% CI 0.59 to 0.97), and accuracy was 77% (95% CI 0.62 to 0.92).

Detection of multivessel CAD based on multivessel pattern of abnormalities. Inducible perfusion abnormalities occurred more frequently in multivascular regions than did wall motion abnormalities (44% vs. 18%, p = 0.001). Defects were detected in ≥2 vascular distributions in 64 of 95 patients with multivessel CAD and in 10 of 75 patients without multivessel CAD (sensitivity = 67%, 95% CI 58 to 77; specificity = 87%, 95% CI 79 to 94; and accuracy = 76%, 95% CI 70 to 82). New or worsening wall motion abnormalities were detected in ≥2 vascular distributions in 27 of the 95 patients with multivessel CAD and in 3 of 75 patients without multivessel CAD (sensitivity = 28%, 95% CI 19 to 38, $p < 0.001$; specificity = 96%, 95% CI 92 to 99, $p < 0.05$; and accuracy = 58%, 95% CI 51 to 66, $p < 0.001$). Figure 1 presents echocardiographic images of a patient who developed perfusion defects in the LAD and LCx territories at the intermediate and peak stress stages, whereas wall motion was abnormal only in the LAD distribution at peak stress.

Regional accuracy. Table 4 presents accuracy of both techniques for the regional diagnosis of CAD. Sensitivity and accuracy of MCE were significantly higher in all vascular regions. However, the difference in sensitivity was larger for RCA and LCx compared with the LAD territory. The majority of perfusion abnormalities occurred at an intermediate stage of DSE, often without wall motion abnormalities, resulting in a larger difference in sensitivities between both techniques at an intermediate as compared with peak stress. When CAD was defined as a ≥70% stenosis, sensitivity improved for each technique in all vascular regions. MCE maintained a higher sensitivity for diagnosis of RCA and LCx CAD, whereas sensitivity of

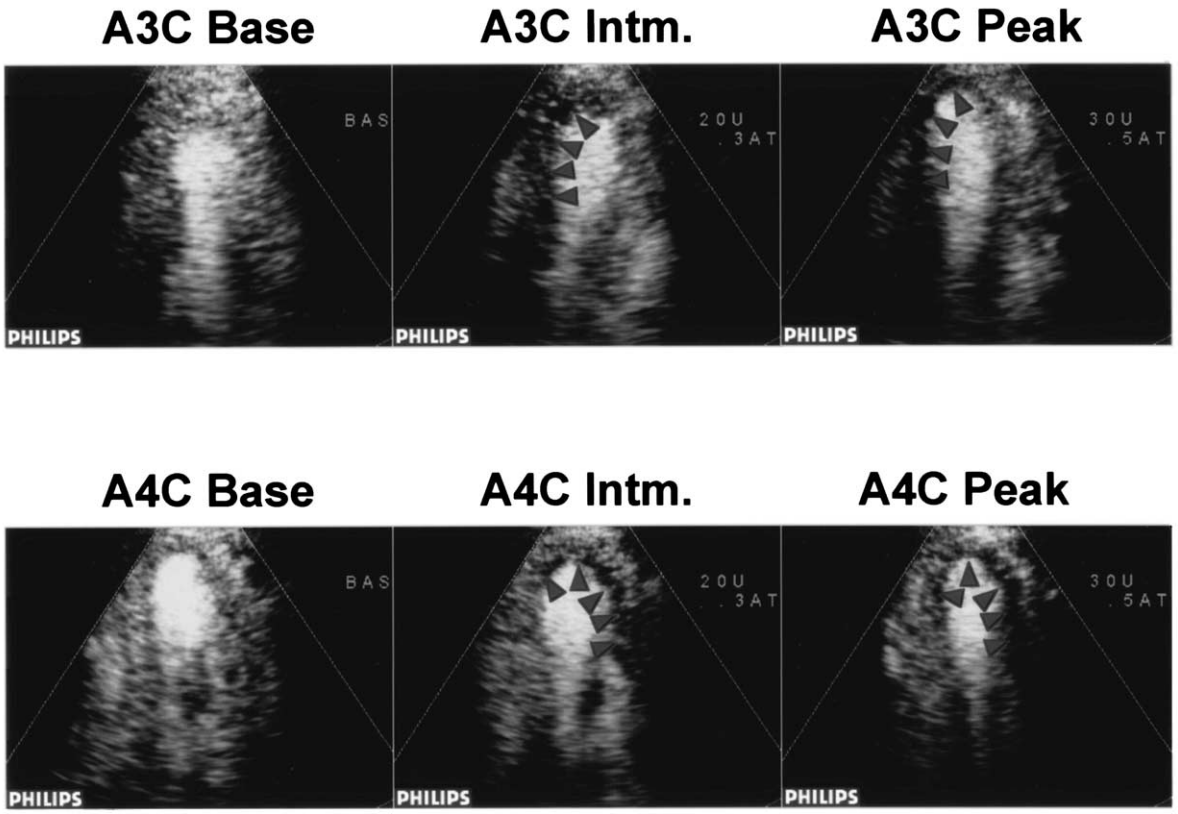

Figure 1. Echocardiographic images from the apical four-chamber and three-chamber views, at rest, intermediate stage (Intm), and peak stage of dobutamine stress in a patient with left anterior descending (LAD) and left circumflex (LCx) coronary artery disease (CAD). Perfusion abnormalities were evident in the lateral, posterior, and apical segments at intermediate phase with extension of these abnormalities at peak stress **(arrows)**. The patient had inducible wall motion abnormalities confined to the apex at peak stress.

Table 4. Regional Accuracy of Myocardial Contrast Echocardiography and Wall Motion Analysis for the Diagnosis of Coronary Artery Disease in the Three Major Arterial Regions

Arterial Region/Diagnostic Parameter	Myocardial Contrast	Wall Motion	p
LAD			
Sensitivity at peak stage	78% (70–86)	63% (53–73)	0.008
Sensitivity at intermediate stage	60% (51–70)	22% (14–30)	0.0001
Sensitivity for ≥70% stenosis	87% (78–95)	82% (70–90)	NS
Specificity	72% (62–83)	80% (70–89)	0.09
Accuracy	76% (70–82)	70% (62–77)	0.04
RCA			
Sensitivity at peak stage	64% (54–75)	33% (23–44)	0.0001
Sensitivity at intermediate stage	47% (36–59)	8% (4–17)	0.0001
Sensitivity for ≥70% stenosis	67% (54–81)	43% (29–57)	0.01
Specificity	89% (82–95)	99% (93–100)	0.004
Accuracy	77% (71–83)	67% (59–74)	0.02
LCx			
Sensitivity at peak stage	77% (68–86)	37% (27–48)	0.0001
Sensitivity at intermediate stage	60% (48–70)	12% (5–19)	0.0001
Sensitivity for ≥70% stenosis	80% (69–91)	42% (40–52)	0.0001
Specificity	83% (67–86)	97% (89–99)	0.004
Accuracy	81% (74–86)	67% (59–74)	0.002
Pooled sensitivity for stenosis ≥50%	74% (69–79)	46% (40–52)	0.001
Pooled sensitivity for stenosis 50–69%	67% (58–76)	30% (21–38)	0.0001
Pooled sensitivity for ≥70% stenosis	79% (72–85)	57% (49–64)	0.001

Diagnostic parameters are presented as % with corresponding 95% confidence intervals.

both techniques for diagnosis of LAD stenosis was equally high (Table 4). Differences in regional sensitivity were narrower for stenoses ≥70% (22%) compared with stenoses between 50% and 69% (37%) (Fig. 2).

DISCUSSION

In this study, we compared the accuracy of WMA and MCE during DSE for the overall and regional diagnosis of CAD in 170 patients who underwent coronary angiography. The use of MCE resulted in a significant improvement in overall and regional sensitivity as well as negative predictive value for the diagnosis of CAD. Differences in sensitivity between both techniques were larger at the intermediate phase of the stress test. Although the specificity of WMA was higher, the overall accuracy and regional accuracy were significantly higher for MCE.

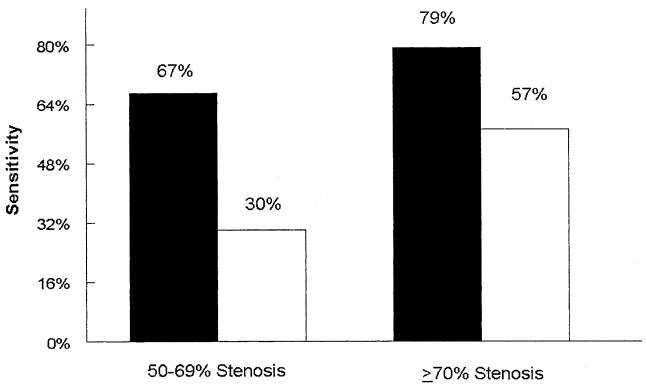

Figure 2. Pooled regional sensitivities of wall motion analysis and myocardial contrast echocardiography for the diagnosis of coronary stenoses between 50% and 69% and ≥70%. **Solid bars** = perfusion; **open bars** = wall motion.

Impact of stress level on the sensitivity. Failure to achieve the target heart rate has been reported as a cause of false negative DSE studies in patients with CAD (1,5,8). However, 10% to 20% of patients still fail to achieve the target heart rate because of premature termination of the test or inadequate chronotropic response (1,23). Myocardial perfusion abnormalities on radionuclide imaging have been detected in patients with CAD in the absence of wall motion abnormalities at a lower level of dobutamine stress (5,8,24,25).

Our study showed that reversible myocardial perfusion abnormalities could be detected in patients with CAD by real-time MCE. The majority of these abnormalities were observed without concomitant wall motion abnormalities at an earlier stage of the test. These findings would suggest that MCE can enhance the sensitivity and accuracy of DSE in patients who fail to achieve the target heart rate, as well as in patients in whom the test needs to be prematurely terminated because of side effects. Our study also emphasizes the concept of the ischemic cascade during demand stress in humans, in that inducible myocardial perfusion abnormalities preceded wall motion abnormalities during ischemia, as has already been shown in animal studies (9).

Recognition of multivessel CAD. Recognition of multivessel CAD has important therapeutic and prognostic implications. Although the majority of patients with multivessel CAD demonstrate wall motion abnormalities during DSE, these abnormalities are frequently localized to one vascular region (1). The sensitivity of DSE for identifying

multivessel CAD based on wall motion abnormalities in multivascular regions has ranged from 8% to 71% (1). In our study, MCE had a higher sensitivity for recognition of multivessel CAD (67% vs. 28%), with only a modestly lower specificity (87% vs. 96%) compared with WMA. These findings suggest that MCE may be a better method for evaluating the extent of CAD and predicting which patients have the largest functional area at risk.

Diagnostic accuracy in the three coronary arterial distributions. Previous studies have demonstrated a modest sensitivity for DSE in diagnosing significant CAD in an individual coronary artery as well as in patients with single-vessel CAD (1–7). In this study, MCE had a significantly higher sensitivity and accuracy than WMA for the diagnosis of LAD, RCA, and LCx CAD. The difference in sensitivity was larger in the RCA and LCx regions. Previous studies have also confirmed the lower sensitivity of WMA in detecting isolated RCA or LCx disease when compared with isolated LAD disease (7). One explanation for the smaller differences in LAD sensitivity is the larger myocardial region subtended by LAD, which tends to make the identification of WMA less difficult. Leong-Poi et al. (9) studied nine dogs that underwent either single- or multivessel stenosis placement. In single-vessel stenosis, abnormal perfusion was seen at the lowest dose of dobutamine irrespective of the stenosis severity, whereas a wall motion abnormality was seen only at high doses of dobutamine and was influenced by the stenosis severity. The spatial extent of abnormal perfusion exceeded that of the wall motion abnormality at all but the highest dobutamine dose. Thus, the enhanced regional sensitivity we observed with MCE may be due to both the earlier occurrence of a perfusion defect and the greater size of any induced perfusion defect.

Impact of coronary artery stenosis severity. When CAD was redefined as ≥70% stenosis, sensitivity was enhanced for both techniques in all arterial regions. Sensitivity of MCE remained higher than that of WMA for the diagnosis of LCx and RCA disease, whereas sensitivities for LAD CAD were no different. Pooled results in the three arterial regions showed a higher sensitivity for MCE for stenoses between 50% and 69% as well as for stenoses ≥70%. However, differences in regional sensitivity were smaller for stenoses ≥70% compared with stenoses between 50% and 69%. These data, as well as previous published reports, indicate that perfusion abnormalities during stress occur with less severe stenosis diameters than those that induce wall motion abnormalities (26,27). Animal studies have confirmed this phenomenon by demonstrating that dobutamine induces capillary derecruitment distal to a noncritical coronary stenosis, and that graded coronary stenoses result in a progressive reduction of myocardial blood flow ratios while wall thickening remains normal (28,29).

Study limitations. Coronary angiography was performed according to the discretion of the treating physician and not per study protocol. The study patients represented only 13% of patients who underwent DSE. Therefore, results are heavily biased toward the selection process. This may explain the higher prevalence of CAD in the study patients and the lower specificity of MCE, because ischemia was more frequently detected by MCE, leading to more verification bias in association with perfusion abnormalities.

The lower specificity of MCE could also be due to artifactual defects in the apical and basal segments due to near field destruction and lung interference (30). Also, it is possible that impairment of vasodilator reserve may occur in the absence of a significant major coronary arterial narrowing. Although wall motion analysis was performed with the aid of contrast-enhanced border detection, which increases the number of segments that can be analyzed during DSE (31), the use of frame rates between 25 and 30 Hz may have decreased the ability of the reviewer to detect tardokinesis as a sign of ischemia (32).

Patients in this study had a high pre-test probability of CAD, reflected by 75% prevalence. This possibly contributed to a high sensitivity of MCE. The sensitivity of MCE may be lower in a population with lower disease prevalence.

Two different MCE agents were used, with potential differences in bubble concentration. However, adjustments were made in the dose administered to account for these differences, and a separate analysis of both agents revealed no difference in the diagnostic accuracy.

We used a small bolus injection technique to analyze myocardial perfusion. Unlike a continuous infusion of microbubbles, a bolus injection may have greater attenuation and will not be able to quantify myocardial blood flow changes (33). Most investigators consider the infusion method as the ideal way to achieve a "steady-state" microbubble concentration in the cavity pool and thus a constant input function. This also avoids the cavity attenuation that may occur when bolus injections are used at the higher cardiac outputs during staged dobutamine/atropine studies. However, with the very small bolus injections used in this study, we reduced the attenuation that occurs from left ventricular cavity contrast and had feasible image interpretation in 95% of patients. It is more likely that the majority of the attenuation problems were related to the low mechanical index pulse sequence schemes used for real-time imaging. Although a continuous infusion could potentially have improved the detection of coronary stenoses during dobutamine infusion, the reductions in myocardial blood volume alone from a coronary stenosis were sufficient to produce a significant improvement in accuracy using a simple bolus injection technique.

SUMMARY AND CONCLUSIONS

Real-time MCE improves the sensitivity and accuracy of DSE for the overall and regional diagnosis of CAD compared with WMA. The majority of reversible perfusion abnormalities in patients with CAD occur at the intermediate phase of the stress test, often without wall motion abnormalities, emphasizing the concept of an ischemic

cascade during dobutamine stress in humans. Therefore, MCE will be particularly useful in patients who cannot achieve the target heart rate. The sensitivity of MCE is higher for detection of multivessel CAD based on abnormalities in ≥2 arterial regions, which can potentially improve the identification of high-risk patients. The findings of our study suggest that MCE should be the preferred method whenever the patient is anticipated not to achieve the target heart rate and in patients in whom the benefit of very high sensitivity outweighs the disadvantage of lower specificity, such as those with a pre-test probability of CAD higher than 50%. Future studies are needed to determine whether MCE can improve the prognostic value of DSE.

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